Tools for teaching genetics in an OBGYN Residency Program

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Introduction

- Genetics is the study of biologic variation
- Medical genetics is the application of this study of biologic variability to human health and disease

Learning Objectives

- Recognize that Medical Genetics is an important part of the practice of Obstetrics and Gynecology
- List the major topics in genetics that should be covered in the 4-year OBGYN residency curriculum
- Identify Institutional resources that provide standards for genetics education and services
- Identify Web based resources in Medical Genetics

Where can Genetics be incorporated into the OBGYN training program?

- Basics of Genetics
  - Chromosome
  - Molecular
- Pre-conception Care
- Obstetrics
  - Genetic counseling
- Gynecology
- Women's Health Care

Chromosome structure and function

- Histones, chromatin, nucleosomes, centromere, telomeres, satellites
- Euchromatin, heterochromatin, constitutive heterochromatin, facultative heterochromatin
- Mitosis
- Meiosis
- Recombination

Chromosomal basis of inheritance

- Numerical abnormalities
  - aneuploidies - trisomy 13, 18, 21
  - sex chromosomal abnormalities
- Structural abnormalities
  - insertions, deletions, inversions (paracentric, pericentric),
  - translocations - Robertsonian, recipricol, balanced, unbalanced
- Contiguous gene syndromes

Chromosomal basis of inheritance

- What chromosome abnormalities are most commonly seen in first trimester loss?
- What patients are at increased risk for chromosome abnormalities?
- What ultrasound clues identify the fetus with chromosome abnormalities?
- What screening and diagnostic tests are available for chromosomal abnormalities during pregnancy?

Molecular Genetics

- **DNA structure and function**
  - replication, transcription, translation
- **Classes of DNA**
  - Organization of genes
- **mRNA, tRNA**
- protein structure
- mitochondrial DNA
- polymorphisms, dinucleotide repeats, SINEs, LINEs
- mutations, loss of function, gain of function, dominant negative

Control of gene expression

- the operon
- genomic imprinting
- DNA methylation
- X inactivation
- Isodisomy

Mendelian Inheritance

- Autosomal Recessive Inheritance and Disorders
  - pedigree analysis and example cases
- Autosomal Dominant Inheritance and Disorders
  - pedigree analysis and example cases
- Sex Linked Recessive and Dominant Inheritance and Disorders

Non-Mendelian Inheritance

- Mitochondrial Inheritance and Disorders
- Multifactorial Inheritance and Disorders
- Mosaicism
- Uniparental Disomy
- Trinucleotide repeats and genetic instablity
- Imprinting

Non-Mendelian Inheritance

- Penetrance
- Expressivity
- Anticipation
- Sex Influence
- Sex Limitation
- Pleitropy
- Phenotypic and Genetic Heterogeneity

Mendelian Inheritance

- What are some of the common inherited conditions that will be seen in Pregnancy?
  - Cystic Fibrosis (Current recommendations for Cystic Fibrosis Testing ACOG, ACMG, ASHG)
  - Sickle cell disease, thalassemias, hemophilias
  - Triplet Repeat Disorders - Fragile X as a cause of Mental Retardation, Huntington's Disease, other Neurological disorders

Molecular Genetics: Clinical Applications

- Karyotype: chromosome analysis and banding
- FISH, painting, cloning, PCR
- Southern blots, northern blots, western blots, immunohistochemistry
- SSCP, direct sequence analysis
- ASO, dot blot
- RFLP analysis, linkage
- UPD, deletion analysis

Methods of studying genetic changes in populations

- Linkage Analysis
- Gene Mapping and the Human Genome Project
- Pharmacogenetics
- Human Major Histocompatibility Complex and Disease Susceptibility
- Gametogenesis
- Twinning (dizygotic, monozygotic) and timing

Genetic Counseling

- Definition of counseling
- Mendelian Inheritance and Genetic Counseling
- Testing for family history of mental retardation
- Non-directive counseling
- Risk Assessment

Goals of Genetic Counseling

- Education about the medical facts (diagnosis, prognosis, management options)
- Education about mode of inheritance , recurrence risks, penetrance, expressivity, and availability of genetic testing
- Education about pregnancy and reproductive options
- Supporting the family as they choose a course of action
- Helping family to adjust to the condition

Genetic Counseling - Indications

- advanced maternal age, advanced paternal age
- exposure to teratogens
- patient, partner or family member with a history of genetic disorder, birth defect or mental retardation
- fetal anomaly
- recurrent pregnancy loss
- high risk populations: African, Acadian, Eastern European Jewish, Mediterranean or SE Asian ancestry

Genetic counseling process

- How to draw a three-generation pedigree
- Genetic Assessment and Pedigree Analysis (three generation pedigree, medical history, medical record review, physical examination)
- Risk assessment (Bayesean analysis)
- Genetic education (non-directive counseling)
- Psychosocial issues (psychological burdens, shame, guilt, cultural and socioeconomic differences, counselor biases)

Genetic counseling process

- Problems in genetic counseling may include genetic heterogeneity, phenotypic heterogeneity nonpaternity, sporadic cases, incomplete penetrance, variable expressivity
- what questionaire tools are helpful in preparing the family history?
- What computer-assisted tools are available for pedigree construction?
  - Progeny
  - Cyrillic

Ethical Issues in Genetics

- autonomy/confidentiality versus beneficence
- autonomy/confidentiality versus nonmalificence
- autonomy versus paternalism
- gene therapy
- genetic screening

Obstetrics - What should we learn?

- Genetic screening
  - maternal serum screening
- Preconception counseling
- Human malformations
- Reproductive options
- Medico-legal issues

Genetic screening

- Definition and goal, screening criteria, test characteristics, sensitivity, specificity, positive and negative predictive values, cost effectiveness
- 2x2 tables
- test sensitivity and test specificity
- positive predictive value and negative predictive value
- test limitations

Genetic screening

- Environmental (radiation, alcohol, drugs)
- Advanced Maternal Age
- Advanced Paternal Age
- Family History (Three generation pedigree)
- Population Based screen

Maternal Serum Screening

- Maternal Serum Screening
- First trimester biochemical and/or Nuchal Translucency
- Second trimester biochemical screening
- “Genetic Ultrasound”
- ACOG Technical Bulletin – Maternal Serum Screening – **www.acog.org**

Preconception counseling

- Genetic risks and prior pregnancy risks
- Nutritional aspects - folic acid, avoidance of alcohol and tobacco
- occupational risks and exposures
- infectious risks – e.g. toxoplasmosis precautions

Prenatal Counseling

- Advanced maternal or paternal age
- Abnormal maternal serum screen
- Fetal anomalies
- Recurrent pregnancy loss
- High risk populations
- Family history genetic disorders, birth defects, mental retardation, teratogen exposure

Teratology - Viral infections, medications, drug exposures

- What are the known human teratogens?
  - Medications (include Vitamin A)
  - Virus (CMV, Toxo, Parvovirus, Rubella)
- What is the timing of exposure?
- Why is this timing important?
- REPROTOX website – **www.reprotox.org**

Population Screens

- Some populations at higher risk than others
  - Cystic Fibrosis
  - Sickle Cell anemia
  - Tay - Sachs
  - Canavan’s disease
  - Neimann Pick
  - Gaucher
  - Thalassemias

Recurrent Pregnancy Loss - etiology and evaluation

- What is the definition of RPL?
- What tests should be offered?
- What treatments are available?
- What are the most common causes of RPL?
- What women are at increased risk for this complication of pregnancy?
- What tests should be offered to couples with this history?

Mental Retardation

- What are the most common causes of Mental Retardation
- What causes are identifiable?
  - Fragile X syndrome and its variants
  - Down syndrome

Human Malformations

- normal embryologic and fetal milestones and development
- homeobox genes
- developmental fields
- abnormal development
- differentiation
- cell death
- developmental timing

Human Malformations

- malformation
- malformation sequence
- deformation
- disruption
- aplasia, hypoplasia, dysplasia
- major and minor anomalies
- associations
- syndromes

Multifactorial Inheritance

- Open Neural Tube Defect (ONTD)
- Cleft Lip and/or Palate (CL/P)
- Congenital Heart Disease (CHD)
- Club feet
- Congenital Hip Dysplasia

Risk Calculations

- AR, AD, XLR, XLD, mitochondrial disorders
- Multifactorial disorders
- Bayessian Analysis

Prenatal Testing

- Pre-implantation genetic diagnosis
- Amniocentesis, Chorionic Villus Sampling
- PUBS, placental biopsy
- FISH

Reproductive options

- adoption
- Pre-implantation genetic diagnosis
- Termination of pregnancy
- special needs adoption
- altered Obstetric and/or Pediatric management
- fetal therapy
- **Medico-legal and ethical considerations**

Gynecologic, Surgical, and Primary Care Genetics

- Cancer
- Cardiovascular Disease and Pulmonary
- Thrombophilias and bleeding diathesis
- Connective Tissue Disorders
- Hematologic Disorders
- Renal and metabolic disorders
- Genetic Disorders of the Endocrine System
- Neurological disorders
- Anesthetic considerations

Cancer

- Molecular Basis of Cancer
- Cell cycle, Viral oncogenes, retroviruses
- Tumor biology, clonal nature of cancer
- Proto-oncogenes, Oncogenes, Tumor suppressor genes
- Acquired cancers, genetic alterations, cancer cytogenetics (translocations and oncogenesis)
- Heritable cancers, Knudson two hit hypothesis
- Acquired Tumors and Cancers

Heritable Cancer Syndromes

- clinical characteristics (BRCA1&2, HNPCC, LFS)
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- Symptomatic versus Pre-symptomatic testing
- Genetic Counseling issues
- Ethical and legal issues
- Management

Cardiovascular Disease

- Molecular basis for cadiovascular disease
- Normal and abnormal lipid metabolism
- Normal and abnormal coagulation and hemostasis
- Normal and abnormal connective tissue composition and physiology

Cardiovascular Disease

- Familial Hypercholesterolemia, combined familial hyperlipidemia
- ApoE, ApoA1, Homocysteinemia, ApoB, MTHFR
- Hyperlipoproteinemia types I, II
- Familial hypertryglyceridemia
- factor II (prothrombin)

Cardiovascular Disease

- clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity, and polymorphisms)
- molecular biology and physiology
- Symptomatic vs. Presymptomatic testing
- Genetic Counseling issues
- Ethical and legal issues

Thrombophilias

- Leiden factor V
- antithrombin III
- protein C
- protein S
- prothrombin (factor II)
- MTHFR
- homocysteinemia
- antiphospholipid symdrome

Thrombophilias

- clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- molecular biology and physiology
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- Genetic Counseling issues
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Bleeding diathesis

- VWD
- Hemophilia
- Factor V, X deficiency
- Factor VII deficiency
- Glanzman’s thrombasthenia
- Wiskott Aldrich

Bleeding diathesis

- clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- molecular biology and physiology
- Symptomatic versus Presymptomatic testing
- Genetic Counseling issues
- Ethical and legal issues
- Management

Connective Tissue Disorders

- Marfans syndrome and Ehlers - Danlos syndrome
- molecular biology and physiology clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity polymorphisms)
- Symptomatic vs. Presymptomatic testing

Hematologic Disorders

- The Hemoglobinopathies and Thalassemias
- molecular biology and physiology clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- Symptomatic versus Presymptomatic testing

Renal Disorders

- Renal Cystic Disorders, Congenital Disorders of the Urinary Tract, Wilms Tumor
- molecular biology and physiology, and clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- Symptomatic versus Presymptomatic testing

Endocrine System Disorders

- Type II DM
- Thyroid disorders
  - Autosomal Dominant Hyperthyroidism
  - Familial Graves Disease and Hashimoto Thyroiditis
- Multiple Endocrine Deficiency
- Medullary Thyroid Carcinoma
- molecular biology and physiology clinical characteristics
- risk identification (high risk screening)
- Symptomatic vs. Presymptomatic testing

Pulmonary Disorders

- alpha 1 - antitrypsin deficiency
- cystic fibrosis, asthma
- molecular biology and physiology clinical characteristics
  risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- Symptomatic vs. Presymptomatic testing

Metabolic Disorders

- Hemochromatosis
- Wilson’s disease
- molecular biology and physiology, clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity, polymorphisms)
- Symptomatic vs. Presymptomatic testing

Neurologic Disorders

- Fragile X
- Myotonic Dystrophy
- Huntington Disease
- Alzheimer Disease
- molecular biology and physiology, and clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity and polymorphisms)
- Symptomatic vs. Presymptomatic testing

Anesthesia Issues

- Malignant Hyperthermia
- Acetylcholinesterase Deficiency
- clinical characteristics
- risk identification (high risk screening)
- genetics (genes, loci, inheritance, penetrance, expressivity, polymorphisms)
- molecular biology and physiology
- Symptomatic vs. Presymptomatic testing

Medical Organizations on the Web:

- ACGME – www.acgme.org
- CREOG – www.creog.org
- ASHG -www.faseb.org/genetics/ashg/ashgmenu.htm
- ACOG – www.acog.org
- ABOG – www.abog.org
- AMA – www.ama-assn.org
- NIH Consensus Panels – www.nih.org

Genetic Information Sites

- OMIM – www.ncbi.nlm.nih.gov/omim
- GeneClinics – www.geneclinics.org
- Ethics -www.nhgri.nih.gov/ELSI
- March of Dimes - www.modimes.org/HealthLibrary2/portal.htm
- Contact a family charity – www.cafamily.org.uk
- USU - www.usuhs.mil/genetics

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